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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/708,786	11/08/2000	Sudhir Agrawal	47508.700	2469

23483 7590 01/30/2007

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EXAMINER	
GIBBS, TERRA C	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	01/30/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 01/30/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/708,786	AGRAWAL, SUDHIR	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *September 18, 2006 and November 6, 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,6,8-11,14,15,17-20,23,24,26,27 and 29-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,8-11,14,15,17-20,23,24,26,27 and 29-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed September 18, 2006 and November 6, 2006.

Claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 24, 26, 27, 29-34 are pending in the instant application.

Claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 24, 26, 27, 29-34 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Nucleotide and/or Amino Acid Sequence Disclosure

Applicant's amendment to the specification filed September 18, 2006 to include sequence identifiers is acknowledged. It is noted that the instant application meets the requirements of 37 CRF §1.821 through 1.825.

Response to Amendment

Applicant's Amendment filed November 6, 2006 to provide a current listing of the pending claims is acknowledged.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed April 17, 2006, claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 24, 26, 27, 29-34 were rejected under 35 U.S.C. 103(a) as being

unpatentable over Koike et al. (Cancer Research, 1997 Vol. 57:5475-5479) in view of Miraglia et al. [U.S. Patent No. 6,184,212 B1]. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed April 17, 2006.

Response to Arguments

In response to this rejection, Applicants argue that before any burden falls to Applicant to determine and provide evidence that the combination of the teachings of Koike et al. and Miraglia et al. would or would not have the additional functional limitation of "statistically significantly potentiating the activity of the prodrug", the Office Action must establish that there is motivation to combine the cited references. Applicants contend that such a motivation to combine is lacking from the previous Office Action mailed April 17, 2006.

In response to Applicant's argument that there is no suggestion to combine the references, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, combining and modifying the teachings of the prior art to produce the claimed invention is found in the references themselves and in the knowledge generally available to one of ordinary skill in the art. For example, and in reiteration to the previous 35 U.S.C. 103(a) art rejection

of record (see Office Action mailed April 17, 2006), one or ordinary skill in the art would have been motivated to devise a method for statistically significantly potentiating the activity of an SN-38 prodrug, the method comprising co-administering an oligonucleotide, for the purpose of altering drug sensitivity (e.g. additive or synergistic effect) as taught by Koike et al. One of ordinary skill in the art would have been motivated to take the antisense oligonucleotide taught by Koike et al. and make it a more traditional and conventional size, including from about 5 to about 15 or from about 13 to about 100 nucleotides in length, for ease of synthesis and delivery to cells in culture as taught by Miraglia et al. Furthermore, it is well known in the art that longer antisense oligonucleotides, such as the one taught by Koike et al., are difficult to transfect in cells in culture. Therefore, One of ordinary skill in the art would have been motivated to take the antisense oligonucleotide taught by Koike et al. and make it from about 5 to about 15 or from about 13 to about 100 nucleotides in length since these lengths are traditionally and conventionally well known in the art to provide ease of synthesis and delivery to cells *in vitro*. Therefore, it is the Examiner's position that the Office Action has established that there is clear motivation to combine the teachings of Koike et al. with those of Miraglia et al. to establish the teachings of the instant application.

Applicants also argue that Koike et al. do not describe the co-administration of an oligonucleotide and a SN-38 drug. Instead, Applicants contend that Koike et al. describe cells transfected with an expression vector having a 805bp transcript

complementary to cMOAT that is synthesized *in situ* followed by the administration of CPT-11 to these cells.

This argument and contention have been fully considered but are not found persuasive. The Examiner agrees that Koike et al. teach cells transfected with an expression vector having a 805bp transcript complementary to cMOAT that is synthesized *in situ* followed by the administration of CPT-11 to these cells. However, the issue is that the claims recite, "comprising", which is open-ended language. For more explanation, see MPEP 2111.03 where it states, "The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps". Therefore, the claims do not exclude the cells transfected with an expression vector having a 805bp transcript complementary to cMOAT that is synthesized *in situ* followed by the administration of CPT-11 to these cells as taught by Koike et al. Thus, given the open-ended language of the claims, Koike et al. clearly teach the co-administration of an oligonucleotide and a SN-38 drug.

Applicants further argue that Miraglia et al. fail to provide the teachings that Koike et al. lacks. Applicants argue that Miraglia et al. describe antisense oligonucleotides, however, Miraglia is silent with regards to the co-administration of an antisense oligonucleotide and a SN-38 prodrug.

These arguments have been fully considered, but are not found persuasive because in the previous Office Action mailed April 17, 2006, the reference of Miraglia et al. was not relied upon to teach the co-administration of an antisense oligonucleotide

and a SN-38 prodrug. Instead, Miraglia et al. was relied upon to teach that it is well known and routine in the art to design use antisense oligonucleotides from about 5 to about 15 or from about 13 to about 100 nucleotides in length. Further, Miraglia et al. was relied upon to teach the routine nature of modifying the antisense oligonucleotide for the purpose of increasing stability in the presence of nucleases. However, in an attempt to fully satisfy Applicant's arguments, Miraglia et al. actually teach the co-administration of an antisense oligonucleotide and a SN-38 prodrug. For example, Miraglia et al. teach at columns 11 and 12, lines 54-67 and 1-19, respectively, that antisense oligonucleotides are administered in conjunction with other traditional therapeutic modalities, including chemotherapeutic agents, in order to increase the efficacy of a treatment regimen. While Miraglia et al. do not explicitly mention that the chemotherapeutic agent is a SN-38 prodrug, CPT-11 (irinotecan) and other SN-38 prodrugs are within the scope of their invention, since, at the time of filing, CPT-11 was well known in the art to be a chemotherapy agent.

Applicants also argue that Miraglia et al. describe antisense oligonucleotides targeted to mdm-2, whereas Koike et al. discusses antisense oligonucleotides to cMOAT. Applicants contend that mdm-2 is an ubiquitin ligase for p53 and plays a role in targeting a protein for degradation, while cMOAT is a cell membrane anion transporter protein, which plays a substantially different role in multidrug resistance than mdm-2. Applicants argue that one skilled in the art would not have any reason to believe, based upon the teachings of Koike et al., that co-administration of antisense for a ubiquitin ligase with irinotecan (CPT-11) would be successful.

This argument has been fully considered, but is not found persuasive. First, the Examiner would like to note that Koike et al. are silent as to whether or not the co-administration of antisense for an ubiquitin ligase with irinotecan (CPT-11) would successfully potentiate the activity of the prodrug. Nowhere do Koike et al. discuss the potentiating effect of oligonucleotides targeted to mdm-2 or an ubiquitin ligase.

Second, regarding Applicants argument that one skilled in the art would not have any reason to believe that co-administration of antisense for a ubiquitin ligase with irinotecan (CPT-11) would be successful, the Examiner would like to direct Applicants to the arguments and remarks made [by Applicant] earlier during prosecution history of the instant application. For example, Applicant's arguments and remarks filed August 13, 2003 discusses that Example 2 of the instant application demonstrates that "oligonucleotides produce a statistically significant potentiating effect on Camptosar that is independent of the sequence of the oligonucleotide" (emphasis added) (see page 12, first full paragraph). Furthermore, Applicant's arguments and remarks filed March 5, 2004 discusses that Example 1 demonstrates the potentiation of Oligo 2 occurs in a target sequence-independent manner" (see page 7, second full paragraph). The Examiner would also like to point Applicant to the instant specification at page 15, second full paragraph where it explicitly discloses, "These results demonstrate that oligonucleotides produce a statistically significant potentiating effect on Camptosar that is independent of the sequence of the oligonucleotide". Therefore, Applicants own remarks and disclosures explicitly teach that potentiation occurs in a **target sequence-independent manner**.

Applicants further argue that it appears that the previous Office Action mailed April 17, 2006 is examining the claims in a "problem-solution approach", which has the danger of using hindsight.

In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

At the time the claimed invention was made, Koike et al. clearly taught enhancing CPT-11 drug sensitivity comprising the co-administration of an antisense oligonucleotide. Therefore, the knowledge of potentiating the activity of a SN-38 prodrug, such as CPT-11, comprising co-administering an oligonucleotide was explicitly taught in the prior art and was not gleaned from Applicant's disclosure.

Thus, it is maintained that the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

tcg
January 18, 2007

JOAN MCGARRY
PRIMARY EXAMINER
AU 1635